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REVIEW ARTICLE

Adenosine and Adenosine Receptors in the Immunopathogenesis and Treatment of Cancer†

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Abstract

Tumor cells overcome anti-tumor responses in part through immunosuppressive mechanisms. There are several immune modulatory mechanisms. Among them, adenosine is an important factor which is generated by both cancer and immune cells in tumor microenvironment to suppress anti-tumor responses. Two cell surface expressed molecules including CD73 and CD39 catalyze the generation of adenosine from adenosine triphosphate (ATP). The generation of adenosine can be enhanced under metabolic stress like tumor hypoxic conditions. Adenosine exerts its immune regulatory functions through four different adenosine receptors including A1, A2A, A2B, and A3 which are expressed on various immune cells. Several studies have indicated the overexpression of adenosine generating enzymes and adenosine receptors in various cancers which was correlated with tumor progression. Since the signaling of adenosine receptors enhances tumor progression, their manipulation can be promising therapeutic approach in cancer therapy. Accordingly, several agonists and antagonists against adenosine receptors have been designed for cancer therapy. In this review, we will try to clarify the role of different adenosine receptors in the immunopathogenesis, as well as their role in the treatment of cancer.

Keywords: Adenosine, adenosine receptors, cancer, immunopathogenesis, treatment

Introduction

Cancer cells exhibit several features including high proliferation, immunosuppression, resistance against apoptosis, high replicative immortality, neoangiogenesis, and metastasis. The immortality of malignant cells demonstrates the failure of the host anti-tumor immune responses to control the growth and metastasis processes. Cancer cells induce an immunosuppressive microenvironment in which they can freely expand and growth (Khalil et al., 2016; Mahoney et al., 2015). Various immune cells such as regulatory T (Treg) cells (Jadidi-Niaragh et al., 2013), myeloid derived suppressor cells (MDSCs) (Yazdani et al., 2015), type II natural killer T (NKT II) cells (Ghalamfarsa et al., 2013), and tumor associated macrophages (M2 macrophages) are involved in the immunosuppression process (Cui et al., 2016). Soluble factors such as inhibitory cytokines [interleukin (IL)-10, IL-35, transforming growth factor (TGF)-β)], hypoxia inducible factor (HIF), and adenosine are other important immunosuppressive factors that help to tumor progression (Kitamura et al., 2015). Regarding the important role of the immune system in the tumor progression, immune modulating factors such as adenosine may be considered as the crucial determinants for tumor development. It has been shown that the concentration of adenosine is significantly increased (10–20-fold higher than normal situation) in tumor microenvironment, which may help to cancer progression (Blay et al., 1997). Adenosine is a purine nucleoside that is released from cells or generated extracellularly following cleavage of adenosine 5′-triphosphate (ATP) by two cell surface enzymes including CD73 and CD39 (Jadidi-Niaragh et al., 2016). Adenosine can suppress various immune cells involved in anti-tumor responses and promote the development of immunosuppressive cells such as Treg and MDSCs through binding to adenosine receptors (Antonioli et al., 2013). It is demonstrated that a transient or chronic hypoxia which is appeared in solid tumors enhances the accumulation of adenosine in tumor area (Blay et al., 1997). Inhibition of anti-tumor responses by adenosine has been reported by several investigators both *in vitro* and *in vivo* (Gessi et al., 2002; Hoskin et al., 1994a; Hoskin et al., 1994b; MacKenzie et al., 2002). Most recently, we have been shown that inhibition of adenosine production can significantly arrest tumor growth, *in vivo* (Jadidi-Niaragh et al., 2017). Moreover, it is suggested that blockage of adenosine receptors through specific antagonists can be potent promising therapeutic approach for cancer therapy (Fredholm, 2007; Raskovalova et al., 2005). In this review, we tried to clarify the role of adenosine and adenosine receptors in the cancer development as well as their therapeutic potentials.

Adenosine receptors

There are four subtypes of adenosine receptors (ARs) in humans, including A1R, A2AR, A2BR, and A3R that each receptor exhibits distinct pharmacological properties, cell and tissue distribution, and secondary effector signaling (Cronstein, 1994). ARs are members of seven transmembrane glycoproteins family coupled with G proteins and are extensively distributed throughout the body. There is about 49% homology between A1 and A3 and 59% between A2A and A2B receptors. While A1, A2A and A3 receptors show high affinity, A2B has low affinity for adenosine binding (Ciruela et al., 2010). Initial classification of ARs into A1 and A2 was based on pharmacological analyzes such as affinity to their ligands, different responses to ligands and response to methylxanthines (Calker et al., 1979; Londos et al., 1980). The heterogeneity of A2Rs had led to their classification into A2AR and A2BR based on high affinity of A2AR and low affinity of A2BR to adenosine in the rat brain (Daly et al., 1983). A1R gene in human is located on 1q32.1 (Megson et al., 1995) and in mouse (Yaar et al., 2005) is on chromosome 1. A1R sequence is more conserved among species than other ARs (Ramkumar et al., 1991). A2A gene is on human chromosome 22q11.23 (Deckert et al., 1997; Dubey et al., 1996; MacCollin et al., 1994) and on mouse chromosome 10 (Yaar et al., 2005). This 410 amino-acid receptor (409 amino-acids in mouse) is the largest AR due to its extended carboxy terminal (Jacobson et al., 1997; Piersen et al., 1994). The A2B and A3 genes are on human chromosomes 17p12-11.2 (Jacobson et al., 1995) and 1p21-p13 (Atkinson et al., 1997) and on mouse chromosomes 11 and 3, respectively (Yaar et al., 2005). A3R is the only AR that was cloned before discovering its pharmacological identifications (Meyerhof et al., 1991). Interestingly, A3R was the first cloned as an orphan receptor (Meyerhof et al., 1991) and then as a methyl-xanthine sensitive AR in rat (Zhou et al., 1992), xanthine sensitive AR in sheep (Linden et al., 1993) and finally as an relatively xanthine sensitive AR in human (Linden, 1994; Sajjadi and Firestein, 1993; Salvatore et al.,

1993). The most diversity is seen on A3R which has 30% diversity in its amino-acids between human and rat (Yaar et al., 2005). In human, A1R is mainly expressed in the central nervous system (CNS), whereas A2BR and A3R are expressed mainly peripherally and involved in inflammation and immune responses. A2AR is expressed in both the CNS and peripheral, so it can regulate both the neurologic and immunologic responses (Fredholm et al., 2005; Haskó et al., 2009b; Lane et al., 2011; Linden, 2011; Ohta and Sitkovsky, 2001). It has been shown that various classes of proteins including serine-threonine or tyrosine protein kinases, β-arrestins and scaffolding proteins can bind to ARs (Ciruela et al., 2010). Signaling of ARs is usually cytoprotective in various tissues under a wide variety of physiological conditions (Fredholm et al., 2001b; Fredholm et al., 2011). A1 and A3 receptors signals are mediated through Gi and Go members of G proteins family and decrease cAMP levels. On the other hand, A2A and A2B receptors stimulate adenylyl cyclase trough Gs protein and increase cAMP levels. Moreover, A2BRs can also stimulate phospholipase C via Gq protein (Ji and Jacobson, 1999). It has also been reported that ARs can also exert their signaling through the activation of mitogen-activated protein kinase (MAPK) signaling pathway in some cell types which resulted in stimulation of extracellular signal-regulated kinase1 (ERK1), ERK2, JUN kinase and P38 kinase (Graham et al., 2001; Hoskin et al., 2008; Raman et al., 2007; Schulte and Fredholm, 2000). The signaling pathways of ARs are illustrated in figure 1.

All four human ARs have been cloned and characterized (Ferré et al., 2009; Ginés et al., 2000; Kong et al., 2012; Libert et al., 1992; Peterfreund et al., 1996; Pierce et al., 1992; Salvatore et al., 1993; Weiß and Grisshammer, 2002). The human A2AR was the first non-rhodopsin, non-adrenergic GPCR for which an X-ray crystallographic structure was identified (Jaakola et al., 2008) and led to design of selective agonist and antagonist drugs (Carlsson et al., 2010; Katritch et al., 2010). The three-dimensional structure of other ARs has been predicted and efforts for their crystallization and investigation of their roles in diseases in order to design of new potent AR ligands are going on.

The role of Adenosine in cancer

Since the solid tumors are usually deprived from the sufficient oxygen, tumor cells are under hypoxic condition. Hypoxia enhances a adenine nucleotide breakdown, which then leads to increased concentration of adenosine in tumor microenvironment (Vaupel et al., 1989). Accordingly, it is reported that the adenosine level is significantly increased in the extracellular fluid of solid tumors (Blay et al., 1997). It has been thought that secretion of adenosine following hypoxic condition leads to enhancement of angiogenesis which will promote tumor growth. Although there are controversial reports regarding the effect of adenosine on the release of angiogenic factors (Burnstock, 2002), it seems that it increases the secretion of vascular endothelial growth factor (VEGF) (Grant et al., 1999) and promotes the proliferation of endothelial cells (Burnstock, 2002; Van Daele et al., 1992). The stimulatory effects of adenosine on the DNA synthesis (Ethier et al., 1993) and endothelial cell migration (Lutty et al., 1998) more substantiate the angiogenesis promoting properties of this factor.

In contrast to angiogenic-promoting effects of adenosine, there is evidence which indicates that adenosine enhances apoptosis process in the human leukemia HL60, melanoma A375, and astrocytoma cells at mM concentrations through the intracellular actions of adenosine rather than surface receptors (Tanaka et al., 1994). However, it is demonstrated that the inhibitory effect of adenosine on tumor growth is limited to its low concentrations (lower than 25 mM) (Fishman et al., 2001), because in high concentrations (100 mM) this inhibition was progressively reversed (Khoo et al., 1996). Moreover, it is suggested that the inhibitory effect of adenosine on tumor growth is mainly through the cytostatic mechanism rather than an apoptotic process (Fishman et al., 2001). It seems that adenosine at μM concentrations can directly inhibit the proliferation of cancer cells and tumor-promoting role of adenosine is mediated through its immunosuppressive effects on anti-tumor responses (Fishman et al., 1998).

Adenosine inhibits the induction and development of cytotoxic T lymphocytes and the anti-tumor function of NK cells (MacKenzie et al., 2002; Williams et al., 1997). Adenosine plays an important role in the intrathymic apoptotic deletion of T cells during development (Barbieri et al., 1998b). Moreover, deletion of adenosine form thymocytes culture by adenosine deaminase led to increased proliferation of these cells (Sandberg, 1983). On the other hand, it is reported that adenosine impairs the induction of mouse cytotoxic T lymphocyte, without

affecting their survival (MacKenzie et al., 2002). In addition to direct inhibition of anti-tumor lymphocytes, adenosine can also suppress T cell priming in part through suppression of IL-12 and TNF-α production by dendritic cells (DCs) and macrophages (PANTHER et al., 2001). Moreover, adenosine suppresses M-CSF-mediated proliferation of murine bone marrow-derived macrophages (Xaus et al., 1999).

As discussed above, it seems that when adenosine is generated at high levels, similar to what observed in tumor microenvironment, it inhibits anti-tumor function of both lymphocytes and APCs to help tumor growth. The inhibitory effects of adenosine on lymphocyte proliferation in cancer patients is significantly higher than normal individuals (Bajaj et al., 1983) which may be in part due to upregulation of ARs on lymphocytes derived from cancer patients. Therefore, blockage of the pathways leading to adenosine production such as CD39 and CD73 or inhibition of ARs may be considered as potent therapeutic approach for cancer therapy. The overexpression of ARs in all reported cell lines and the role of ARs in cancer cells are listed in tables 1 and 2, respectively. It should be noted that the reported expression levels of ARs are mRNA expression and not protein due to incompleteness of the protein expression data of ARs. Moreover, the databanks of mRNA expressions are consistently being updated and the expression of mRNA and protein of ARs in many cell lines is yet to be determined. Studies have noted that the low mRNA expression is not predictive of the presence of ARs on cell surface due to post-transcriptional mechanisms which determine the rate of protein expression and also due to specific mRNAs or proteins the half-lives. (Audic and Hartley, 2004; Gessi et al., 2007; Gygi et al., 1999; Weinzierl et al., 2007). So, it would be better to report protein expression rather than mRNA expression. For instance, the mRNA expression of A3R in colon cancer cell lines were low, while in protein level, the most expression was for A3R (Gessi et al., 2007) but due to incomplete and incomprehensive information of protein expression in comparison with mRNA expression, the mRNA expressions are reported.

It would be noteworthy that the effect of ARs on increasing or decreasing proliferation of cells is dose-dependent. For example, in colorectal carcinoma and colon cancer cell lines the effect of ARs in proliferation was totally dose-dependent (Gessi et al., 2007) and also in high dose, adenosine might decrease the proliferation and induce apoptosis in breast cancer cell lines (Hashemi et al., 2005). The mechanisms of these dose-dependent effect is not fully understood but it might be to some extent due to desensitization or occupation of other ARs in high dose of adenosine or ARs agonists (Trincavelli et al., 2002).

Adenosine receptors in cancer

A1Rs in cancer

Although several studies attempted to clarify the role of A1R in cancer progression, its precise function during tumor development is elusive. It is demonstrated that the expression of A1R is increased in colorectal adenocarcinomas and peritumoural colon tissues (Khoo et al., 1996). Upregulation of A1R has also been demonstrated in the human leukemia Jurkat and human melanoma A375 cell lines (Gessi et al., 2001; Merighi et al., 2001).

The anti-proliferative effects of A1R agonists have been shown in the human LoVo metastatic (D'Ancona et al., 1993) and TM4 cell lines (Shaban et al., 1995). Similar results were demonstrated following stimulation of A1R in MOLT-4, T47D, HS578T, and MCF-7 cell lines (Mirza et al., 2005; Woodhouse et al., 1998).

Adenosine helps to tumor cells chemotaxis which may be effective in tumor metastasis process. It should be noted that this chemotaxis could be inhibited by A1R-antagonist (Woodhouse et al., 1998).

Anti-apoptotic and pro-survival effects of A1R in normal cells have also been reported (Lee and Emala, 2002; Liu et al., 2002). In contrast, there is evidence implying the pro-apoptotic effects of A1R in primary cultured rat astrocytes and in C6 glial cells (Appel et al., 2001; Di Iorio et al., 2002). Moreover, it is reported that A1R do not affect the proliferation and survival of A375 human melanoma cells (Merighi et al., 2002).

While the cisplatin upregulates the expression of A1R in the rat kidney (Bhat et al., 2002), it is reported that A1R antagonists exert contradictory functions in the cisplatin-induced nephrotoxicity (Bhat et al., 2002; Heidemann et al., 1989; Knight et al., 1991). Moreover, overexpression of this receptor has also been demonstrated in MDA-MB-468 human tumor cell lines where downregulation of A1Rs by siRNA attenuates both cell growth and proliferation and enhances cell death and apoptosis (Mirza et al., 2005). The increased expression of A1Rs has also been found in the tumor microenvironment in the F98 glioma-bearing rats (Bauer et al., 2005). Expression of A1R in rat brain tumors and in rat C6 glioma cells has been detected in different investigations (Castillo et al., 2007; Dehnhardt et al., 2007).

In another study, Synowitz and coworkers reported that depletion of A1R was associated with vigorous development of experimental glioblastoma and strong infiltration of microglial cells around the tumors. Expression of A1R was also increased on tumor-resident microglia compared to microglia in the unaffected brain tissue. They also found A1R on microglia from human glioblastoma resections. Although the use of A1R agonists in organotypical brain slice cultures inhibited tumor growth, depletion of microglial cells from the slices led to tumor growth which implies that adenosine-mediated inhibition of glioblastoma progression depends on activation of A1 in microglial cells (Synowitz et al., 2006).

It has also been demonstrated that A1R signaling can enhance cell death in the rat astrocytoma cells in part through activation of caspases 3 and 9 (Sai et al., 2006). Similarly, adenosine could induce apoptosis in the CW2 human colonic cancer cells by activating caspases 3, 8 and 9. This effect was inhibited by an A1R antagonist. Moreover, intraperitoneal administration of adenosine into CW2 bearing mice led to tumor arrest through inducing apoptosis via A1Rs (Saito et al., 2010). A recent study also showed the influence of adenosine on the epithelial integrity and inhibition of inflammation through A1R in healthy endometrium. It is reported that downregulation of adenosine through blockage of CD73 and A1R signaling is associated with the progression of endometrial carcinoma (Bowser et al., 2016). This was the first report that claimed inhibition of CD73 and adenosine signaling lead to tumor progression. Therefore, it seems that inhibition of adenosine, ARs or adenosine producing enzymes may be considered with respect to the tumor type or disease stage.

A2ARs in cancer

There is no comprehensive data regarding the physiological functions of A2AR including protection against apoptosis and toxic insults. However, it is known that A2ARs are involved in the anti-ischemic action of adenosine (Vossler et al., 1997). A2ARs are expressed on hematopoietic cells and inhibit generation of inflammatory mediators in activated macrophages, neutrophils, DCs, NK cells and lymphocytes (Raskovalova et al., 2006; Scheibner et al., 2009; Schnurr et al., 2004; Visser et al., 2000). Among the four AR subtypes, A2AR exerts the most immunosuppressive functions. Hence, deletion of A2AR results in the higher and lethal inflammation in response to moderate stimuli compared to other ARs. A2AR signaling can potently inhibit TCR-induced cytokine production (Raskovalova et al., 2007) and induce anergy in $CD4^+$ T cells (Zarek et al., 2008). Administration of A2AR agonists into inflammatory autoimmune experimental models could also attenuate disease progression which implies anti-inflammatory function of A2AR (Odashima et al., 2005). It is well known that A2AR has indispensable effect in the control of inflammation, *in vivo* (Ohta and Sitkovsky, 2001). Ligation of A2AR on immune cells, such as macrophages, T cells, DCs and NK cells can suppress their effective functions such as cytotoxicity and secretion of pro-inflammatory cytokines (Hoskin et al., 2008; Schnurr et al., 2004; Sullivan, 2003). In addition, signaling of A2AR in NK cells can hamper tumor cell death through FasL, geranzyme and perforin as well as inhibit the production of pro-inflammatory cytokines IFN-γ, TNF-α, IL-2, MIP-1α, M-CSF and G-CSF (Beavis et al., 2013; Lokshin et al., 2006; Raskovalova et al., 2006). The influence of A2AR on MAPK signaling may be in part related to cAMP level-dependent and -independent mechanisms (Klinger et al., 2002). Therefore, A2AR signaling suppresses the function of both $CD4^+$ and $CD8^+$ T cells (Naganuma et al., 2006; Sevigny et al., 2007). In the view point of $CD4^+$ T cell subsets, A2AR signaling blocks the generation of TH1 and TH17 cells and induces the development of Treg cells (Zarek et al., 2008).

In vivo studies have been shown that blockage of A2ARs is associated with neuroprotective outcome, thereby it seems that A2AR signaling may be detrimental in neurons (Ongini and Schubert, 1998). There are some controversies about the pro- or anti-apoptotic effects of A2AR which may be in part related to the cell type, degree of receptor activation, and/or coupling to different transduction mechanisms (Cassada et al., 2001).

The expression of A2ARs have been detected on the surface of various human tumor cells, such as SH-SY5Y neuroblastoma, NG108-15 neuroblastoma x glioma hybrid, U937 monocytic lymphoma, Jurkat T-cell leukemia, A431 epidermoid cells, A375 melanoma, colon carcinoma HT29 and DLD-1 cells, U87MG human glioblastoma cells, and human breast cancer MCF-7 cells (Etique et al., 2009; Gessi et al., 2001; Hillion et al., 2002; Merighi et al., 2001). It has been shown that A2A agonist enhances the proliferation of MCF-7 cells and also can interfere with the ethanol-induced activation of estrogen receptor (ER) signaling (Etique et al., 2009). A2AR has also been increased in hepatocellular carcinoma and ligation of A2AR in Hep3B cells can increase the expression of erythropoietin both *in vitro* and *in vivo* (Fisher and Brookins, 2001; Nagashima and Karasawa, 1996). It is demonstrated that A2AR signaling in tumor infiltrating T cells leads to suppression of their anti-tumor response (Koshiba et al., 1997). Accordingly, A2AR deficient mice showed increased antitumor immune

responses via $CD8^+$ T cells, which was associated with tumor growth arrest. Moreover, it is reported that adenosine-resistant effector T cells, generated through exposure of activated T cells to non-selective AR agonist, N-ethylcarboxamidoadenosine NECA, are more effective in adoptive immunotherapy (Ohta et al., 2009). Based on above discussed studies, it seems the development of A2AR antagonists may be an effective strategy to overwhelm immunosuppressive effects of adenosine in the tumor microenvironment.

Adenosine facilitates the wound healing process in part through enhancement of angiogenesis in response to tissue injury via A2AR (Montesinos et al., 2002; Montesinos et al., 1997). There are also other studies implying the angiogenic effects of adenosine, *in vivo* (Leibovich et al., 2002; Sexl et al., 1995; Sexl et al., 1997). Thus, it seems that tumor protecting effects of A2AR is not limited to suppression of anti-tumor responses and it can promote tumor growth through angiogenic effects. It should be noted that angiogenesis is an important factor for tumor metastasis. Accordingly, it is reported that A2AR signaling can promote the proliferation of endothelial cells which leads to enhanced angiogenesis and tumor metastasis (Lutty and McLeod, 2003). So, it seems that administration of A2AR antagonists may be associated with downregulation of tumor growth in part through blockage of angiogenesis and metastasis.

A2BRs in cancer

Although the A2BR is expressed in many tissues, the precise physiological features of A2BR are not fully described. It is found that only high concentrations of adenosine (under pathophysiological conditions) can activate A2BR. While the stimulation of A2BR can induce apoptosis in arterial smooth muscle cells (Peyot et al., 2000), its signaling inhibits death of mesencephalic dopaminergic neurons (Michel et al., 1999). It has also been demonstrated that adenosine suppresses the proliferation of macrophages in an A2BR-dependent manner (Xaus et al., 1999). The crucial role of A2BR in tumor progression has been shown in various solid tumors such as bladder, breast, colon and prostate tumors (Cekic et al., 2012; Ma et al., 2010; Wei et al., 2013). Overexpression of A2BR has been observed in oral squamous cancer cells (OSCC) which was associated with tumor progression (Kasama et al., 2015).

There is evidence implying the angiogenic effect of A2BR (Feoktistov et al., 2002), particularly in the human retinal endothelial cells (HREC) (Grant et al., 1999). A2BR signaling promotes the neovascularization process through upregulation of angiogenic growth factors such as VEGF, IL-8, and basic fibroblast growth factor (bFGF) (Feoktistov et al., 2002; Merighi et al., 2007b; Zeng et al., 2003), however, other ARs enhance angiogenesis without increasing VEGF (Koszałka et al., 2016). A2BR signaling can affect the maturation and function of DCs (Novitskiy et al., 2008; Yang et al., 2010b). A2BR signaling during the generation of DCs from monocytes leads to appearance of the peculiar phenotype of DC (Novitskiy et al., 2008), which can promote angiogenesis by producing VEGF (Novitskiy et al., 2008). Ligation of A2BR can also reduce the secretion of gamma interferon (IFN-γ) and CXCL10 (Antonioli et al., 2013). Moreover, stimulation of A2BR enhances the growth and proliferation of endothelial cells (Dubey et al., 2002; Grant et al., 1999). Blockage of A2BR affects the E-selectin and ICAM-1 expression on endothelial cells, which leads to modulation of leukocyte adhesion and rolling (Yang et al., 2006). Increased plasma leakage and neutrophil infiltration in tissues has also been demonstrated in the A2BR-deficient hypoxia mice model (Eckle et al., 2008), which implies an important role of A2BR in maintenance of endothelium integrity in hypoxia condition (Haskó et al., 2009a). Thus, it seems that application of A2BR antagonists may be a useful approach for *in vivo* suppression of angiogenesis process in tumor.

It has been shown that A2BR signaling inhibits the ERK-1/2 signaling pathways which results in growth inhibition (Bieber et al., 2008). The high expression of A2BRs in some tumor cells such as an ER negative breast cancer cell line MDA-MB-231 and their antiproliferative effects make these receptors as the promising target for cancer therapy (Dhillon et al., 2007). While the inhibition of angiogenesis needs to the use of A2BR antagonists, growth inhibition through ERK1/2 requires to A2BR agonists. So, there is a dilemma in which we should investigate the relative importance of each pathway for tumor progression before therapeutic suggestions can arise.

A2BR deficient mice show decreased tumor growth and increased survival time after inoculation with Lewis lung carcinoma which was associated with significantly reduced levels of VEGF compared to control mice (Ryzhov et al., 2008). Therefore, it seems that there is close relation between A2BR on tumor cells, VEGF, and tumor progression, implying the higher importance of angiogenic effects of A2BR compared to ERK-1/2 inhibition.

There are also other studies indicating the role of A2BR in regulation of secretion of some inflammatory cytokines such as IL-6 (Fiebich et al., 1996) and IL-8 (Merighi et al., 2009), however, it should be further investigated.

Vecchio *et al.* have recently been reported that A2BR can significantly enhance the proliferation of prostate tumor cell lines through constitutive adenosine-independent function, *in vitro* (Vecchio et al., 2016). The AR-independent apoptotic effect of adenosine has also been reported by several investigators. Adenosine kinase can change adenosine to AMP in the cancer cells (Nogi et al., 2012; Sai et al., 2006; Yang et al., 2010a; Yang et al., 2011; Yang et al., 2007). Activation of MAPK pathway by high levels of AMP can lead to activation of caspases 3 and 9 (Sai et al., 2006). Adenosine induces apoptosis through caspase 8-dependent (Yang et al., 2007) or caspase-independent mechanisms (Nogi et al., 2012). Hence, adenosine and ARs exhibit various activities that are independent of each other and this issue should be considered in adenosinergic therapy.

A3Rs in cancer

A3R is a Gi-coupled molecule which can be detected in some human tissues such as lung, liver, brain, aorta, testis and heart (Gessi et al., 2004; Madi et al., 2004). It is reported that A3R signaling can exert both the neuro- and cardio-protective effects (Abbracchio and Burnstock, 1998; Appel et al., 2001; Liu et al., 1994). Expression of A3R has been detected in various tumor cells such as astroglial (Ceruti et al., 1997), murine bone marrow (Fishman et al., 1998) , HL60 and K562 human leukemia (Gessi et al., 2002; Kohno et al., 1996), Jurkat lymphoma (Gessi et al., 2001), U937 monocytic macrophagic human cell lines (Yao et al., 1997), Nb2 rat lymphoma (Fishman et al., 2002), A375 human melanoma (Merighi et al., 2001), PGT-b mouse pineal gland tumor cells (Suh et al., 2001), human glioblastoma (Gessi et al., 2010; Merighi et al., 2006), and human prostatic cells (Jajoo et al., 2009).

A3R has the low expression in the normal tissues, whereas its expression is significantly increased in tumor cells (Suh et al., 2001), so it may be considered as tumor marker. However, there is no comprehensive comparative study related to the expression levels of A3Rs on normal and tumor tissues. Accordingly, it is demonstrated that the expression of A3R is increased in colorectal cancer which was associated with disease progression (Gessi et al., 2004). There are similar reports regarding the increased expression of A3R in different malignant tumors including human melanoma, colon, breast, small-cell lung, and pancreatic carcinoma (Bar-Yehuda et al., 2008; Madi et al., 2004; Morello et al., 2008). Upregulation of A3R has also been detected in peripheral blood mononuclear cells (PBMCs) which were derived from the hepatocellular carcinoma patients compared to normal individuals (Bar-Yehuda et al., 2008). A3Rs display a sustained expression on tumor cells and can affect on proliferation and cell death (Gessi et al., 2001; Suh et al., 2001). It has recently been reported that A3R signaling is associated with pro-survival effects in human melanoma cells (Merighi et al., 2002). There is also evidence which indicates that only low levels of adenosine exert anti-apoptotic effects through A3R and its high levels induce apoptosis via engagement of A3Rs (Brambilla et al., 2000; Fishman et al., 2000b; Gao et al., 2001; Kim et al., 2002). Moreover, it is elaborated that A3R signaling is principally dependent on the cell- or tissue-specific context (Kim et al., 2002). It has also been suggested that A3R signaling in tumor cells leads to mainly cytostatic rather than apoptotic effects, in a dose dependent manner (Brambilla et al., 2000).

On the other hand, it is reported that muscle tissues are resistant to tumor metastasis which was related to the A3R signaling (Fishman et al., 1998). The mechanism by which A3R exerted this function was in part through the inhibition of telomerase activity and cell cycle arrest in the G0/G1 phase, which resulted in cytostatic effect in Nb2-11C lymphoma cells (Fishman et al., 2000b). Moreover, A3R can attenuate tumor progression through the modulation of WNT pathway (Fishman et al., 2004). WNT pathway, which enhances tumor cell proliferation, is regulated by glycogen synthase kinase (GSK)-3β that is pivotal for β-catenin phosphorylation. The β-catenin promotes the expression of genes such as c-myc and cyclin D1 that are involved in cell cycle progression. Exposure of tumor cells to A3R agonists leads to downregulation of A3R and its downstream molecules such as protein kinase A (PKA) and protein kinase B (PKB/Akt). For compensation, GSK-3β goes to be increased, which results in the destabilization of β-catenin and then downregulation of cyclin D1 and c-myc proteins. In addition, it is reported that stimulation of A3R can decrease the metastatic potential of prostate cancer cells *in vivo*, in part through the inhibition of reduced PKA-mediated stimulation of ERK1/2, which leads to lower NADPH oxidase activity and cancer cell invasiveness (Jajoo et al., 2009).

Matrix metalloproteinases (MMPs) play an important role in the metastasis process (Mirshafiey et al., 2014). Accordingly, stimulation of A3R in U87MG human glioblastoma cells leads to upregulation of MMP-9 through the phosphorylation of ERK1/2, c-Jun N-terminal kinase/stress-activated protein kinase (pJNK/SAPK), PKB/Akt, and activator protein 1 (AP-1) which increase tumor cell invasion and metastasis (Gessi et al., 2010). Interestingly, A1R and A3R signaling stopped cell cycle through reduction of cAMP level which was associated with downregulation of PKB/Akt signaling. On the other hand, stimulation of A2AR increased the cAMP level that could also inhibit cell cycle promotion, implying the dual role of cAMP in proliferation (Lyons et al., 2013; Nardin et al., 2014).

It has been shown that adenosine increased the expression of HIF-1α in response to hypoxia in human melanoma, glioblastoma and colon cancer cells, which is in part through the A3R signaling (Merighi et al., 2005a; Merighi et al., 2007a; Merighi et al., 2006). Activation of MAPK pathway through the A3R signaling is responsible for adenosine-mediated upregulation of HIF-1α protein (Merighi et al., 2005a). Upregulation of HIF-1α in solid tumors increases the generation of extracellular adenosine in the positive loop manner (Linden, 2001; Semenza, 2000; Sitkovsky et al., 2004). It is well known that HIF-1 is involved in the promotion of tumor angiogenesis and metastasis (Semenza, 2003).

There are contrasting results regarding the stimulatory (in glioblastoma and colon cancer) (Merighi et al., 2007a; Merighi et al., 2006) or inhibitory (in pheochromocytoma PC12 cells) (Olah and Roudabush, 2000) effects of A3R signaling on the expression of VEGF. It is suggested that A2BR and A3R cooperatively induce the expression of angiopoietin-2 and VEGF in melanoma cells, which enhance angiogenesis process (Feoktistov et al., 2003; Merighi et al., 2005a).

It seems that angiogenic and metastatic effects of A3R signaling are cell, tissue, and tumor type specific. Therefore, designing new therapeutic approaches based on targeting A3R in each tumor type needs to precise investigation of pro- or anti-tumor function of A3R signaling in that tumor.

Adenosine receptor agonists/antagonists and cancer therapeutic approaches

The importance of AR signaling pathways has been demonstrated in the physiological and pathophysiological conditions such as inflammatory conditions, heart attack, ischemia-reperfusion injury, vascular injury, sepsis, respiratory disorders, obesity, diabetes, inflammatory bowel disease, retinopathy, CNS disorders, and cancer (Baraldi et al., 2008). Nonselective AR antagonists such as caffeine, for maintaining wakefulness, and theophylline for treating bronchospasm were the initial manipulating tools for modulation of ARs signaling. Several selective AR agonists and antagonists are underway for a variety of disorders. Physical structure and conjunction of ARs with other receptors (for example, dimerization of A2AR/D2 dopamine receptor in Parkinson's disease) are of important factors that should be considered for pharmacologic manipulation of ARs in various disorders (Canals et al., 2003; Ferré et al., 2009). Several attempts have been devoted for development of selective ligands of all four types of ARs (Ortore and Martinelli, 2010). It should be noted that development of new ligands in animal models must be precisely investigated, because there is a marked species specificity in the ARs for binding with their ligands (Ukena et al., 1986).

Due to action of enzymes such as adenosine deaminase or adenosine kinase and also function of nucleoside transporters, adenosine has a very short half-life (about 1 second) in circulation (Fredholm et al., 2001a; Fredholm et al., 2011; Müller and Scior, 1993). Thus, development of adenosine agonists bypass these limitations and exhibits higher half-life compared to adenosine (Van Troostenburg et al., 2004). Although several AR agonists have been developed so far, however, only one of them (A2AR agonist regadenoson, Lexiscan™) is in clinical use, which is mainly for a diagnostic purpose rather than therapeutic use (Klaasse et al., 2008). AR desensitization, which is downregulation of receptor following the administration of receptor agonist, is another concern which should be considered for development of AR agonists (Klaasse et al., 2008). Most of the AR agonists are purine nucleosides derivatives, including adenosine or xanthosine (Beukers et al., 2004; Yan et al., 2003). For a long time, adenosine was the single adenosine agonist for treatment of human disorders. Currently, adenosine is selective factor in treatment of paroxysmal supraventricular tachycardia and diagnosis of myocardial perfusion imaging. Furthermore, adenosine has been analyzed in various trials for the treatment of inflammation, neuropathic and perioperative pain, and cardioprotection. It seems that A1R agonists are appropriate for the treatment of cardiac arrhythmia, ischemia, and sleep disorders (Elmenhorst et al., 2007;

Porkka-Heiskanen et al., 2002). Moreover, it has been shown that A2A agonists are associated with anti-inflammatory and immunosuppressive effects (Palmer and Trevethick, 2008). On the other hand, ligation of the A2BR attenuates vascular injury (Yang et al., 2008). Finally, stimulation of A3R is useful in the treatment of autoimmune diseases, such as inflammatory bowel diseases, rheumatoid arthritis and psoriasis and also for cardiac and brain ischemia (Madi et al., 2007; Safarzadeh et al., 2016).

Xanthines analogues were the initial AR antagonists, which exhibited several limitations (Muller and Stein, 1996; Sauer et al., 2000; Weyler et al., 2006).

However, recently developed AR antagonists and prodrug approaches have reduced some of these issues (Müller et al., 2002; Sauer et al., 2000; Vollmann et al., 2008; Weyler et al., 2006). The roles of ARs agonists/antagonists in cancers are listed in table 3.

A1 Adenosine Receptor Antagonists/Agonists

It has been shown that adenosine plays an important role in the regulation of ERα/estradiol (E2) axis which are critical factors in breast cancer growth (Lin et al., 2010). Moreover, E2 could upregulate A1R expression, which was reversible by administration of E2 antagonist ICI (Lin et al., 2010). On the other hand, while the downregulation of A1R in ERα-positive cells decreased E2-dependent proliferation, over-expression of A1R in an ERα-negative cell line increased proliferation. Accordingly, use of A1R antagonist, Dipropylcyclopentylxanthine DPCPX, decreased proliferation and induced P53-mediated apoptosis in MCF-7 cell line (Dastjerdi et al., 2015), which more substantiates the modulatory effect of A1R on E2/ERα-dependent breast cancer growth (Lin et al., 2010). In contrast, the use of A1 agonist, N6-cyclohexyl-adenosine (CHA) and R-isomer of N6 phenyl isopropyl adenosine (R-PIA) was associated with decreased proliferation of tumor cells, in part through the A1R signaling (Hosseinzadeh et al., 2008). On the other hand, another A1 agonist, N6-cyclopen-tyladenosine (CPA), increased the survival and decreased the expression of P53 gene (Dastjerdi et al., 2015). In addition, while the stimulation of A1R in brain, heart and kidney reduced the apoptosis and oxidative cellular damages, A1R antagonists could increase apoptosis and cellular damage following oxidative stress (Lee et al., 2004). As discussed above, it seems that A1R signaling exerts different effects on different tumor types. So, A1R targeted therapy should be designed based on tumor type and A1R signaling outcome.

A2A Adenosine Receptor Antagonists/Agonists

The A2AR signaling in immune cells is associated with immunosuppressive effects, which lead to protection of normal tissues from inflammatory damage. This immunosuppression can be deleterious when tumor cells engage it for escaping from anti-tumor responses (Huang et al., 1997; Sitkovsky et al., 2004; Takayama et al., 1988). Tumor promoting effect of A2AR has been shown in the A2AR-deficient mice which were able to reject inoculated tumors. In recent years, application of A2AR antagonists and A2AR specific siRNAs could significantly inhibit tumor growth, angiogenesis and metastasis processes. Appearance of autoimmunity following melanoma rejection in A2AR-deficient mice more substantiates the immunosuppressive function of A2AR signaling in tumor microenvironment (Ohta et al., 2006).

T cells express high affinity A2A and to a lesser extent low affinity A2B receptors on their cell surface (Apasov et al., 2000). Accordingly, it has been demonstrated that genomic deletion of A2AR in mice leads to complete tumor rejection through the function of $CD8^+$ T cells. Moreover, administration of A2AR antagonists into tumor bearing mice exhibited similar results (Qin and Blankenstein, 2000).

Although the inhibition of A2AR signaling enhances GM-CSF secreting whole cell vaccines, use of these vaccines in phase III trials did not exerted efficacy in prostate cancer (Lassi and Dawson, 2010). However, there are contrasting results in other trials (Nemunaitis et al., 2006).

It has recently demonstrated that administration of soluble B7-DC/FC fusion protein into A2AR- deficient mice could significantly enhance anti-tumor responses (Waickman et al., 2012). These results imply that combination therapy based on inhibition of A2AR and other immunosuppressive molecules and stimulation of immune responses can lead to potent anti-tumor responses.

A2B Adenosine Receptor Antagonists

It has been shown that A2BR deficient mice are resistant against tumor growth which was associated with decreased VEGF production by tumor infiltrating lymphocytes (Ryzhov et al., 2008).

There is evidence implying the tumor promoting function of A2BR signaling. Accordingly, treatment of melanoma bearing mice with A2BR agonist enhanced tumor growth which was associated with increased levels of IL-10 and monocyte chemoattractant protein 1 (MCP-1) and accumulation of MDSCs. In contrast, inhibition of A2BR with PSB1115 could suppress the tumor growth which was associated with downregulation of IL-10 and MCP-1 and MDSCs and upregulation of $CD8^+$ T cells, NKT cells and TH1-like cytokines in melanoma lesions. However, the adoptive transfer of MDSCs could abrogate the ameliorative effects of PSB1115. Thus, it seems that ameliorative effect of A2BR antagonist is in part through the suppression of infiltration of MDSCs into tumor microenvironment (Iannone et al., 2013; Sorrentino et al., 2015). In addition, while the A2BR specific agonist, BAY60-6583, promoted angiogenesis through upregulating VEGF, its selective antagonist, PSB1115, inhibited angiogenesis and enhanced the therapeutic effects of anti-VEGF therapy (Sorrentino et al., 2015).

Wei *et al*. demonstrated that A2BR has highest expression in three commonly used prostate cancer cell lines including PC-3, DU145, and LNCaP compared to other ARs. They showed that the nonselective A2BR agonist NECA and the selective A2BR agonist BAY60-6583, but not the A2AR agonist CGS21680 could increase adenosine 3′,5′-cyclic monophosphate (cyclic AMP) in PC-3 cells. Moreover, NECA could reduce lactate dehydrogenase (LDH) release and caspase-3 activity in PC-3 cells, which were reversible by a selective A2BR antagonist PSB603. Treatment of PC-3 cells with A2BR siRNA blocked NECA-induced proliferation of PC-3 cells. In addition, selective A2BR antagonist PSB603 was able to suppress tumor cell proliferation in all three cell lines. So, it seems that selective A2BR antagonists can be effective therapeutic tools for treatment of prostate cancer (Wei et al., 2013). Furthermore, Wang *et al*. reported that blockage of A2BR expression by miR-128b inhibited the proliferation and migration of gastric cancer cells (Wang et al., 2015).

A2BRs have high expression on MDA-MB-231 breast cancer cells and stimulate adenylyl cyclase activation. While the A2BR nonselective agonists NECA and PHPNECA were able to stimulate tumor cell growth, agonists against other ARs had not significant effects. It has also been demonstrated that A2BR can enhance the migration of tumor cells and metastasis process (Stagg et al., 2010). Accordingly, genetic deletion or pharmacological inhibition of A2BR led to decrease in metastasis *in vitro* and *in vivo* (Desmet et al., 2013). Moreover, the Ca^{2+} A2BR downstream signaling pathway was also blocked by A2BR antagonists, but not with A2A or A3 selective antagonists (Panjehpour et al., 2005). On the other hand, stimulation of A2BR on OVCAR-3 and Caov-4 cell lines by A2BR agonist (NECA) significantly decreased cell viability in a dose-dependent manner. It is demonstrated that NECA induces apoptosis via the mitochondrial signaling pathway. Thus, A2BR agonists may be a potential apoptosis inducer in ovarian cancer cells (Hajiahmadi et al., 2015).

P73 can upregulate the expression of the A2BR. It has recently been demonstrated that p73-mediated upregulation of A2BR significantly enhances apoptosis in cancer cells, in a caspase- and puma-dependent manner. In addition, doxorubicin treated p53-deficient cancer cells upregulate A2BR in a p73-dependent manner. Treatment of these cells with A2BR agonist markedly increased apoptotic death. Therefore, it seems that p73-mediated induction of adenosine signaling can enhance programmed cell death (Long et al., 2015).

A3 Adenosine Receptor Antagonists/Agonists

While the A3R is overexpressed on cancer cells, there is low expression on normal tissues (Gessi et al., 2004; Madi et al., 2004; Ochaion et al., 2009). Accordingly, it is demonstrated that A3Rs are over-expressed in various malignant cells such as leukemia, lymphoma, astrocytoma, melanoma and pineal tumor cells (Gessi et al., 2002; Merighi et al., 2001; Morello et al., 2008; Suh et al., 2001; Trincavelli et al., 2002; Yao et al., 1997). Overexpression of these receptors is also shown in tumor tissues derived from patients with colon, breast, small cell lung, hepatocellular and pancreatic carcinomas, and melanoma (Bar-Yehuda et al., 2008; Gessi et al., 2004; Madi et al., 2004). Furthermore, there was a significant correlation between the increased levels of A3R in tumor tissues and disease progression in breast and colon cancers (Gessi et al., 2004; Madi et al., 2004). Moreover, peripheral blood mononuclear cells (PBMCs) of cancer patients exhibit higher levels of this receptor on their surface compared to normal subjects (Bar-Yehuda et al., 2008; Ochaion et al., 2009). Thus, it seems that A3R may be considered as a therapeutic target and a biological predictive marker in cancer patients. It is suggested

that upregulation of A3R may be in part related to the overproduction of tumor microenvironment factors such as adenosine and cytokines (Keibel et al., 2009; Madi et al., 2007).

The efficacy and safety of A3R agonists have been demonstrated in the phase II clinical studies on inflammatory, ophthalmic and liver diseases (Ariztia et al., 2006; Keibel et al., 2009). It has been shown that adenosine induces a cytotoxic signal in the human breast cancer cell lines MCF-7 and MDA-MB468 via A3R activation that was not seen for other subclasses of adenosine receptors (Panjehpour and Karami-Tehrani, 2007). Accordingly, administration of A3R agonists into animal models of melanoma, prostate, colon and hepatocellular carcinoma was associated with ameliorative effects (Brambilla et al., 2000). It has been shown that A3R agonists can exert effective anti-tumor functions through the regulation of Wnt and NF-κB signaling pathways (Bar-Yehuda et al., 2008; Fishman et al., 2006; Van Troostenburg et al., 2004). Treatment of mice with another A3R agonist IB-MECA downregulated NF-kB expression and increased the infiltration of pro-inflammatory macrophages into tumor microenvironment (Fishman et al., 2003; Fishman et al., 2004; Koszałka et al., 2016). Based on bioinformatic analyses, it is suggested that other transcription factors including c-Rel, MyoD, GR, AP-1, PU.1, GATA-1, C/EBP, CREB, c-fos and c-Jun can bind to the A3R promoter and regulate its expression (Ochaion et al., 2009).

Muscle cells can produce natural agonists of A3R, which may be involved in the rarity of tumor metastasis in muscle (Ochaion et al., 2009). Administration of A3R agonist, 2-Chloro-N(6)-(3-iodobenzyl) adenosine-5'-N-methylcarboxamide (Cl-IB-MECA), could also effectively enhance anti-tumor function of NK cells in part through upregulation of IL-12 in the tumor bearing mice (Fishman et al., 2003; Harish et al., 2003; Mirandola et al., 2004). In contrast, 1-Deoxy-1-[6-[((3-iodophenyl)amino]-9H-purin-9-yl]-N-methyl-β-D-rebofuranuronamide (IB-MECA), another A3R agonist, and Cl-IB-MECA inhibited the growth of various tumor cell lines such as NPA papillary thyroid carcinoma, HL-60 leukemia cells and U-937 lymphoma cells at mM concentration in an A3R-independent manner (Kim et al., 2002; Morello et al., 2008). This controversy is attributed in part to the dose of drug and A3R desensitization. Accordingly, it is suggested that these agonists lose their selectivity at the low doses (Lu et al., 2003; Trincavelli et al., 2002). In vitro studies using these agonists showed that they can suppress the proliferation of various tumor cells such as rat Nb2–11C and mouse Yac-1 lymphoma, K-562 leukemia, B16-F10 melanoma, MCA sarcoma, human PC3 and LN-Cap prostate carcinoma, HCT-116 colon carcinoma and MIA-PaCa pancreatic carcinoma (Fishman et al., 2003; Fishman et al., 2000b; Ohana et al., 2003). However, this inhibitory function could be blocked by A3R antagonists (Madi et al., 2003). A3R agonist could also induce apoptosis in hepatocellular and prostate carcinoma tumor cells through the upregulation of the pro-apoptotic proteins BAD, BAX and caspase-3 (Aghaei et al., 2012; Aghaei et al., 2011; Bar-Yehuda et al., 2008). The apoptotic effects of A3R agonist Cl-IB-MECA have also been demonstrated in rat astrocytes (Abbracchio and Burnstock, 1998) and human astrocytoma ADF cells (Barbieri et al., 1998a), human peripheral blood mononuclear cells, both myeloid and lymphoid cells (U937, HL60, and Jurkat) (Khoo et al., 1996; Yao et al., 1997), and cardiac myocytes (Baraldi and Borea, 2000; Shneyvays et al., 2000; Shneyvays et al., 1998). However, all of the above discussed studies used high agonist concentrations which may affect the receptor specificity. Moreover, high concentrations of A3R agonists may also desensitize A3Rs. There are also other reports implying the anti-proliferative and apoptotic effects of A3R agonists in even micromolar doses of the A3 agonists (Lee et al., 2005; Panjehpour and Karami-Tehrani, 2004). Similar results were reported when melanoma or HL-60 human leukemia cells were treated with Cl-IB-MECA (Kim et al., 2008; Merighi et al., 2005b). More recently, Koszalka *et al.* administered selective agonists of A1R ,A2AR and A3R (CCPA, CGS-21680 and IB-MECA, respectively) into CD73-knockout mice model of melanoma and observed that the tumor inhibitory effects of these agonists at the primary stage of tumor may be blocked by tumor progression and these inhibitory effects could be due to modifications in MAPK signaling pathways (Koszałka et al., 2016). This finding opened a new sight of view that although the use of these ligands has stable effects to promote or limit the tumor and angiogenesis, *in vivo* effects of these ligands may be more complicated and even controversial regarding the type of AR and tumor and also stage of tumor stage. The cordycepin, which is derived from Cordyceps sinensis, a parasitic fungus used in traditional Chinese medicine, could also suppress the growth of murine melanoma and

of Lewis lung carcinoma tumor cells at the even μM concentrations. However, this inhibitory effects could be blocked by the A3R antagonist 3-ethyl-5-benzyl-2-methyl-4-phenylethynyl-6-phenyl-1,4-(±)-dihydropyridine-3,5-dicarboxylate (MRS1191) (Nakamura et al., 2006).

Interestingly, A3R agonists not only inhibit tumor cells, but also help to growth of normal cells and enhance the myelopoiesis in the bone marrow. Since the myelotoxicity is one of the main side effects of chemotherapy, it seems that A3R agonists may be effective drugs for combination therapy with chemotherapeutic drugs. Accordingly, it is reported that administration of A3R agonist in combination with chemotherapeutic agents into tumor-bearing mice inhibited the myelotoxic effects of chemotherapy (Bar-Yehuda et al., 2002). A3R agonists can also be as cardioprotective agents which help us to combine them with some chemotherapeutic drugs such as doxorubicin which exerts acute cardiotoxicity (Zhang et al., 2009).

These characteristics make A3R agonists as potent therapeutic candidate for cancer therapy in combination with chemotherapeutic agents (Fishman et al., 2000a; Merighi et al., 2002; Ohana et al., 2001).

Conclusion

Identification of the precise mechanisms behind the robust immunosuppression exerted by tumor cells can help us to design new therapeutic approaches for cancer therapy. The generation of adenosine is one of the main immunosuppressive mechanisms by which tumor cells not only inhibit anti-tumor responses, but also induce suppressive cells such as Treg cells. So, blocking the adenosine generating enzymes or ARs can be considered as an important therapeutic approach for cancer therapy. It is demonstrated that signaling of A2AR and A2BR in tumor microenvironment can lead to induction and expansion of immunosuppressive cells such as Treg and MDSC. On the other hand, reports regarding the effect of A1R and A3R signaling in tumor biology are controversial (Figure 2). It seems that tumor promoting or tumor limiting effects of these two receptors depend on the tumor type and tumor condition. Several ARs directed agonists and antagonists have been developed and used for treatment of various tumors. We think the use of these agents as monotherapy or in combination with other conventional cancer drugs may lead to promising outcome in the near future.

Conflict of interest statement

None of the authors has any conflict of interest to declare.

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None.

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Figure legends

Figure1. Schematic diagram illustrating possible signaling pathways through ARs. The stimulation of A1R decreases the cAMP via inhibition of adenylate cyclase. A1R stimulates the release of calcium ions from intracellular stores. A1R couples to MAPK pathways, including ERK1,2, PI3K, MEK1 and P38 kinase. The stimulation of A2AR increases the cAMP via activating of adenylate cyclase. A2AR couples to MAPK pathways, including ERK1,2, MEK1, PKA, RAP1 and BRAF. The stimulation of A2BR increases the cAMP via activating of adenylate cyclase. A2BR couples to MAPK pathways, including ERK1,2, PI3K, MEK1, JNK, PKA and P38 kinase.

The stimulation of A3R decrease the cAMP via inhibition of adenylate cyclase. A3R stimulates the release of calcium ions from intracellular stores. A3R couples to MAPK pathways, including ERK1,2, PI3K, MEK1 and RAS. cAMP, cyclic adenosine mono phosphate; Ca, calcium ion; MAPK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; MEK, MAP kinase kinase; PI3K, phosphatidylinositol 3 kinase; PKA, Protein kinase A; RAP, RAS related protein; BRAF, B-Raf Proto-Oncogene Serine/Threonine Kinase; JNK, Jun N-terminal kinase

Figure2. Tumor inhibiting and tumor promoting effects via adenosine receptors stimulation in different tumors. A1R stimulation leads to inhibition of tumors cells proliferation and also leads to apoptosis induction through activation of caspases. In contrast, the pro-tumor effects of A1R stimulation include increase chemotaxis and proliferation in tumors cells. Stimulation of A2A resulted in cell death in some tumors cells. The pro-tumor effects of A2A include increase in angiogenesis through VEGF and some immune-escaping mechanisms shown in the shape. A2B stimulation leads to inhibition of ERK1,2 phosphorylation in tumors cells but its pro-tumor effects of A2B include increase in angiogenesis and in IL-8 and VEGF in several cancers. A3R stimulation has anti-tumor effects via decreasing the cell proliferation and migration in several tumors cells and also has immune-stimulating effects such as induction of G-CSF and IL-12 secretion from immune cells. The A3R pro-tumor effects include increase in VEGF, HIF-1, MMP-9, angiogenesis, migration, proliferation and invasion in cancer cells.

Table1. The overexpression of ARs in human tumor cell lines*

Cell line name	Type of cell line	Adenosine receptors**			
		A1	A2a	A2b	A3
A-431	Epidermoid carcinoma cell line	0.2	0.2	29.6	-
A549	Lung carcinoma cell line	2.6	0.2	16.6	-
AN3-CA	Endometrial adenocarcinoma cell line	0.2	0.1	0.6	-
ASC TERT1	Telomerase-immortalized adipose tissue-derived mesenchymal stem cell line	1.1	-	7.4	-
BEWO	Metastatic choriocarcinoma cell line	0.2	0.7	0.7	-
BJ hTERT+	Adherent BJ fibroblast cell line immortalized with ectopic expression of hTERT	2	1.4	22.7	-
BJ hTERT+ SV40 Large T+	Adherent BJ fibroblast cell line immortalized with ectopic expression of hTERT, transformed with SV40 Large-T infection	0.5	0.5	16.7	-
BJ hTERT+ SV40 Large T+ RasG12V	Adherent BJ fibroblast cell line immortalized with ectopic expression of hTERT, transformed with SV40 Large-T infection, made metastasizing with oncogenic H-Ras	0.3	0.1	21.6	-
CACO-2	Colon adenocarcinoma cell line	23	0.5	7.3	-
CAPAN-2	Pancreas adenocarcinoma cell line	0.6	0.1	30.4	-
Daudi	Human Burkitt lymphoma cell line	-	16.8	3.2	0.1
EFO-21	Ovarian cystadenocarcinoma cell line	6.8	0.4	7.3	-
HaCaT	Spontaneously immortalized keratinocyte cell line	0.1	0.3	45.9	-
HBF TERT88	Telomerase-immortalized adherent brain fibroblast cell line	0.2	-	22.3	-
HDLM-2	Hodgkin lymphoma cell line	-	0.6	9	1.5
HEK 293	Embryonal kidney cell line	1	1.2	16.5	-
HEL	Erythroleukemia cell line	0	0.2	29.3	0.7
HeLa	Cervical epithelial adenocarcinoma cell line	0.1	-	4	-
Hep G2	Hepatocellular carcinoma cell line	-	0.4	8.9	-
HL-60	Acute promyelocytic leukemia cell line	-	0.2	-	0.1
HMC-1	Mast cell leukemia cell line	0.1	2.9	143	89.4
hTCEpi	Telomerase-immortalized corneal epithelial cell line	-	0.1	13.3	-
HUVEC TERT2	Telomerase-immortalized umbilical vein endothelial cell line	-	0.4	6.9	-
K-562	Chronic myeloid leukemia cell line	-	0.2	1.5	-
Karpas-707	Multiple myeloma cell line	-	19.8	0.1	0.1
LHCN-M2	Telomerase-immortalized adherent myoblast cell line	4.4	-	14.6	-
MCF7	Metastatic breast adenocarcinoma cell line	16.3	0.2	6.7	-
MOLT-4	Acute lymphoblastic leukemia cell line	-	6.9	1.8	0.1
NB-4	Acute promyelocytic leukemia cell line	-	0.2	4.1	7.2
NTERA-2	Embryonal carcinoma cell line	9.5	0.1	1.9	-
PC-3	Prostate adenocarcinoma cell line	-	-	23.7	-
REH	Pre-B cell leukemia cell line	-	0.3	-	0.1
RH-30	Metastatic rhabdomyosarcoma cell line	52.4	0.4	0.4	-
RPMI-8226	Multiple myeloma cell line	1.5	22.7	-	-
RPTEC TERT1	Telomerase-immortalized proximal tubular epithelial cell line	22.1	-	13.3	-
RT4	Urinary bladder transitional cell carcinoma cell line	-	0.2	7.3	-
SCLC-21H	Small cell lung carcinoma cell line	0.8	1.2	1	-
SH-SY5Y	Metastatic neuroblastoma cell line	0.8	3.6	1.2	-
SiHa	Cervical squamous carcinoma cell line	4.1	0.2	15.2	-
SK-BR-3	Metastatic breast adenocarcinoma cell line	26.3	5.4	2.6	-
SK-MEL-30	Metastatic malignant melanoma cell line	0.4	-	6.8	-
T-47d	Breast cancer cell line	1.6	0.2	0.1	-
THP-1	Acute monocytic leukemia cell line	0.5	-	3.4	0.3
TIME	Telomerase-immortalized human microvascular endothelial cells	-	-	6.4	-
U-138 MG	Glioblastoma cell line	14.7	1	6.4	-
U-2 OS	Osteosarcoma cell line	9	2.3	18.1	-
U-2197	Malignant fibrous histiocytoma cell line	-	0.5	17	-
U-251 MG	Glioblastoma cell line	8.3	0.1	25	-
U-266/70	Multiple myeloma cell line	-	21	2.1	-
U-266/84	Multiple myeloma cell line	0.1	24.2	-	-
U-698	B-cell lymphoma cell line	-	12.9	-	-
U-87 MG	Glioblastoma, astrocytoma cell line	9.2	1.8	25.3	-
U-937	Monocytic lymphoma cell line	-	3.8	-	-
WM-115	Malignant melanoma cell line	1.2	0.2	9.1	-

*These report is RNA expression of ARs in cell lines based on the Human Protein Atlas data bank of protein and RNA expression, A1R (http://www.proteinatlas.org/ENSG00000163485-ADORA1/cell), A2AR(http://www.proteinatlas.org/ENSG00000128271-ADORA2A/cell), A2BR(http://www.proteinatlas.org/ENSG00000170425-ADORA2B/cell), A3R(http://www.proteinatlas.org/ENSG00000282608-ADORA3/cell)

**The expression rate is calculated by the unit of TPM (Transcripts Per Million)

hTERT. human telomerase reverse transcriptase; SV40. Simian virus 40

Table2. The roles of ARs in malignant tumor's

	A1R	A2AR	A2BR	A3R
Increase proliferation	MDA-MB-468 Breast cancer cell line (Mirza et al., 2005)	MCF-7 Breast cancer cell line (Bieber et al., 2008) , Endothelial cells (Lutty and McLeod, 2003)* , BON-1 pancreatic carcinoma cell line, KRJ-1 Intestinal carcinoma cell line (Kalhan et al., 2012)	Endothelial cells, DU145, LNCaP and PC-3 prostate cancer cell lines (Wei et al., 2013), BON-1 pancreatic carcinoma cell line, KRJ-1 intestinal carcinoma cell line (Kalhan et al., 2012), MB49 bladder carcinoma cell line, 4T1.2 Breast cancer cell line (Cekic et al., 2012)*, 22RV1 prostate cancer cell line (Vecchio et al., 2016), Oral squamous cell carcinoma (Kasama et al., 2015),	HT29, Caco-2 and DLD Colon cancer cell line (Gessi et al., 2007; Sakowicz-Burkiewicz et al., 2013), A375 and C32 Melanoma cell lines (Soares et al., 2014),
Decrease proliferation	L0V0 Colon cancer cell line (D'Ancona et al., 1993), TM4 Sertoli-like cell line (Shaban et al., 1995), MOLT-4 Leukemia cell line, T47D Breast cancer cell line, HS578T Breast cancer cell line (Barry and Lind, 2000), MCF-7 Breast cancer cell line (Dastjerdi et al., 2015), Glioblastoma (Daniele et al., 2014), B16F10 Melanoma cell line (Koszałka et al., 2016)*, D283 Medulloblastoma cell line (Cappellari et al., 2015)*	B16F10 Melanoma cell line (Koszałka et al., 2016)*,	Glioblastoma multiform (Daniele et al., 2014)	CCL228 and Caco-2 Colon cancer cell line? (Polycarpou et al., 2013), Nb-211c and YAC-1 Lymphoma cell line, K-562 and HL-60 Leukemia cell lines, B16F10 Melanoma cell line, MCA Sarcoma cell line (Bar-Yehuda et al., 2001; Fishman et al., 2000b; Fishman et al., 2002), LN-CaP, DU-145 and PC-3 prostate cancer cell lines (Aghaei et al., 2011), MIA-PaCa Pancreatic cancer cell line (Fishman et al., 2003), HCT-116 Colon cancer cell line (Polycarpou et al., 2013) (Sakowicz-Burkiewicz et al., 2013), A375 Melanoma cell line (Merighi et al., 2005b), Breast cancer cells, Lewis Lung cancer cell line, PC12 pheochromocytoma cell line (Nakamura et al., 2006; Panjehpour and Karami-Tehrani, 2004; Panjehpour and Karami-Tehrani, 2007; Vincenzi et al., 2012)
Cell cycle progression and increase cell cycle mediators	MDA-MB-468 Breast cancer cell line (Mirza et al., 2005), HeLa cervical carcinoma cell line (Increase CDK4 and Cycline-E expression) (Mirza et al., 2005)			
Cell cycle arrest				LN-Cap, DU-145 and PC3 prostate cancer cell lines (Aghaei et al., 2011)
Increase apoptosis	MCF-7 Breast cancer cell line (Dastjerdi et al., 2015)		OVCAR-3 and Caov-4 Ovarian cancer cell lines (Hajiahmadi et al., 2015)	LN-CaP, Du-145 and PC-3 prostate cancer cell line (Aghaei et al., 2012), HCT-116 Colon cancer cell line (Sakowicz-Burkiewicz et al., 2013), RCC4-VHL Renal cancer cell line (Nagaya et al.,

				2013), Hepatocellular carcinoma (Stemmer et al., 2013)*, LU-65 and SBC3 Lung cancer cell lines (Kanno et al., 2012; Otsuki et al., 2012), Li-7A, N1S1, Hep-3B Hepatoma cell lines (Bar-Yehuda et al., 2008; Cohen et al., 2011; Wen and Knowles, 2003), Tyroid cancer (Morello et al., 2009), NRK-52E renal tubular epithelial cell line (Kadomatsu et al., 2012), A549 lung type 2 alveolar-like (Kamiya et al., 2012; Varani et al., 2006), Mesothelioma (Nogi et al., 2012)
P27 inhibition	HeLa cervical carcinoma cell line (Mirza et al., 2005)			
Increase caspase-3 and caspase-9	Astrocytoma (Sai et al., 2006)	Caco-2 Colon cancer cell line (Yasuda et al., 2009)		LU-65 Lung cancer cell line (Otsuki et al., 2012),
Decrease Caspases			PC-3 prostate cancer cell line (Cas3) (Wei et al., 2013)	
Increase survival/Decrease apoptosis		HCT-116 Colon cancer cell line (Sakowicz-Burkiewicz et al., 2013),		D384 astrocytoma cell line (Björklund et al., 2008), MCF-7, MDA-MB-468 and MRMT-1 Breast cancer cell lines (Varani et al., 2013), U87MG, A172 glioblastoma cell line (Gessi et al., 2010; Merighi et al., 2007a), 2H3 basophilic leukemia mast cell line (Gao et al., 2001)
Increase cell death		A375 Melanoma cell line (Merighi et al., 2001)		U937 macrophage cell line, HL-60 Leukemia cell line (Sajjadi et al., 1996; Yao et al., 1997),
Increase tumor growth		B16F10 Melanoma cell line (Eini et al., 2015)*, Lung adenocarcinoma (Mediavilla-Varela et al., 2013)*	B16F10 Melanoma cell line (Sorrentino et al., 2015)*	
Increase invasion				A375 and C32 Melanoma cell lines (Soares et al., 2014), U87MG Glioblastoma (Gessi et al., 2010),
Decrease tumor growth and invasiveness				AT6.1 prostate cancer cell line (Jajoo et al., 2009)*, HCT-116 human colon carcinoma cell line, CT-26 murine colon carcinoma cell line (Ohana et al., 2003)*
Increase chemotaxis and migration	A2058 Melanoma cell line (Woodhouse et al., 1998),	Endothelial cells (Montesinos et al., 2002), MDA-MB-231 Breast cancer cell line (Zhou et al., 2015)		A375 and C32 Melanoma cell lines (Soares et al., 2014), HT29 Colon cancer cell line (Merighi et al., 2007b),
Increase metastasis		B16F10 Melanoma cell line (Beavis et al., 2013; Cekic et al., 2014; Mittal et al., 2014)*, 4T1.2 Breast cancer cell line (Beavis et al., 2013)*,	4T1.2 Breast cancer cell line, BL16BL6 Melanoma cell line (Beavis et al., 2013)*, Breast cancer cells (Stagg et al., 2010)*	
Decrease metastasis				Breast cancer cells (bone metastasis) (Varani et al., 2013)* HCT-116 human colon carcinoma cell line, CT-26 murine colon carcinoma cell line (Ohana et al., 2003)*
Increase angiogenesis	B16F10 Melanoma cell line (through increasing VEGFR2) (Koszałka et al., 2016)*	Lung adenocarcinoma (Mediavilla-Varela et al., 2013)*	B16F10 Melanoma cell line (Sorrentino et al., 2015)*	
Increase angiogenic factors and receptors		Endothelial cells (Montesinos et al., 2002)*	Endothelial cells (VEGF, IL-8, bFGF) (Feoktistov et al., 2002), HMC-1 Mast cell line	HT29 colon cancer cell line (VEGF) (Merighi et al., 2007b), A375 Melanoma cell

			(VEGF, IL-8) (Feoktistov et al., 2003), HT29 colon carcinoma cell line (IL-8) (Merighi et al., 2007b), U87MG Glioblastoma (IL-8) (Zeng et al., 2003) , A375 Melanoma (IL-8), B16F10 Melanoma cell line (VEGF) (Merighi et al., 2009) (Sorrentino et al., 2015),	line (angiopoietin-2) (Merighi et al., 2009), U87MG Glioblastoma, HMC-1 Mast cell line (angiopoietin) (Feoktistov et al., 2003), B16F10 Melanoma cell line (VEGFR2) (Koszałka et al., 2016)*
Decrease vascularization, angiogenesis and decrease angiogenic factors/receptors	D283 Medulloblastoma cell line (Cappellari et al., 2015)*	B16F10 Melanoma cell line (VEGFR2) (Koszałka et al., 2016)*		T/C-28a2 chondrocytes (Vincenzi et al., 2013)
Protect endothelial integrity	HEC-1A and HEC-1B Endometrial carcinoma cell line (Bowser et al., 2016)			
Increase immunoescaping		T cell, Glioma (through IL-10, MCP1 and M2 macrophage) (Bergamin et al., 2015), B16F10 Melanoma cell line (through suppression of NK and T cells) (Beavis et al., 2013; Cekic et al., 2014; Mittal et al., 2014)*, Lung adenocarcinoma (T-cell suppression) (Mediavilla-Varela et al., 2013)*	B16F10 Melanoma cell line (through increasing MDSC) (Sorrentino et al., 2015)*	
Increase macrophage tumor infiltration	B16F10 Melanoma cell line (Koszałka et al., 2016)*	B16F10 Melanoma cell line (Koszałka et al., 2016)*		B16F10 Melanoma cell line (Koszałka et al., 2016)*
Increase ERK1/2			GL1 and U87 Glioblastoma (Liu et al., 2014)	
Decrease ERK1/2			MBA-MB-231 Breast cancer cell line (Bieber et al., 2008)	
Increase HIF-1α			Oral squamous cell carcinoma (Kasama et al., 2015)	HT29, Caco-2 and DLD Colon cancer cell lines, A375 Melanoma cell line, U87MG Glioblastoma (Merighi et al., 2005a; Merighi et al., 2007a; Merighi et al., 2006)
Other cytokines/enzymes/ factors		HepB3 Hepatoma cell line (Increase erythropoietin) (Fisher and Brookins, 2001; Nagashima and Karasawa, 1996)*	PC-3 prostate cancer cell line (Decrease LDH) (Wei et al., 2013), Astrocytoma (Increase IL-6), U87MG and A172 Glioblastoma cell lines (Increase MMP-9) (Gessi et al., 2010; Merighi et al., 2007a),	T/C-28a2 chondrocytes and hFOB 1.19 osteoblasts (Decrease IL-6, IL-8, PGE2)(Vincenzi et al., 2013), RAW 264.7, U937 and J774.1 macrophage cell line(Decrease TNF-α and MIP-1α (Martin et al., 2006; McWhinney et al., 1996; Sajjadi et al., 1996; Szabo et al., 1998), XS-106 dendritic cell line (Decrease TNF-α) (Dickenson et al., 2003), BV2 microglia cell line (Decrease TNF-α) (Hammarberg et al., 2003)

*These studies are *in vivo* while the others are *in vitro*

Table3. The role of AR agonists/antagonists in malignant tumors.

Roles of antagonists in tumors	Antagonists	Adenosine Receptors	Agonists	Roles of agonists in tumors
- Decrease proliferation* (Dastjerdi et al., 2015) - Induce p53-mediated apoptosis* (Dastjerdi et al., 2015) - Increase apoptosis and cellular damage following oxidative stress* (Lee et al., 2004)	DPCPX	**A1R**	CHA R-PIA CPA CCPA	- Decrease proliferation* (Hosseinzadeh et al., 2008; Koszałka et al., 2016) - Increase survival* (Dastjerdi et al., 2015) - Decrease p53 expression* (Dastjerdi et al., 2015) - Tumor inhibitory effects* (Hosseinzadeh et al., 2008; Koszałka et al., 2016) - Reduce apoptosis and oxidative stress damages* (Lee et al., 2004) - Increase angiogenesis* (Koszałka et al., 2016) - Induce apoptosis through activation of caspase-3 and caspase-9* (Sai et al., 2006)
- Reduce tumor metastasis and tumor cell migration (Beavis et al., 2013; Mittal et al., 2014; Zhou et al., 2015) - Enhance NK cell activity (Beavis et al., 2013; Mittal et al., 2014) - Increase anti-tumor response (Beavis et al., 2015; Mittal et al., 2014) (Eini et al., 2015; Loi et al., 2013) - Increase T-CD8+ function (Beavis et al., 2015) - reduce tumor-associated T cell numbers * (Cekic and Linden, 2014) - Enhance GM-CSF secreting tumor vaccines (Waickman et al., 2012) - Improve the clinical efficacy of anti-PD-1 and anti-CTLA-4 mAb therapy (Beavis et al., 2015; Iannone et al.,	SCH58261 FSPTP SYN-115 ZM-241385 ANR94	A2AR	CGS-21680	- Immunosuppressive effects* (Beavis et al., 2013; Koszałka et al., 2016) - Tumor promoting effects*(Beavis et al., 2013; Koszałka et al., 2016) - Enhance tumor metastasis* (Beavis et al., 2013) - Inhibit tumor growth, angiogenesis and metastasis* (Koszałka et al., 2016) - Tumor inhibitory effects*(Koszałka et al., 2016)

2014; Mittal et al., 2014)				
- Decrease tumor growth, Proliferation, angiogenesis, migration and metastasis(Beavis et al., 2013; Cekic et al., 2012; Ma et al., 2010; Sorrentino et al., 2015; Vecchio et al., 2016; Wei et al., 2013; Zhou et al., 2015) - Decrease IL-10, MCP-1, TH-1 like cytokines (Iannone et al., 2013) - Decrease MDSC infiltration in tumor (Iannone et al., 2013) - Increase T-CD8+, NKT cells (Iannone et al., 2013) - Increase the effect of anti-VEGF therapy (Sorrentino et al., 2015) - Increase LDH, Caspase-3 (Wei et al., 2013) - Increase IFN-γ and CXCL10 and CXCR+ Tcells (Cekic et al., 2012) - Enhance DC activation (Cekic et al., 2012) - Induce more potent anti-tumor responses (CXCR3-dependent) (Cekic et al., 2012) - Block of Ca2+ downstream signaling pathway (Panjehpour et al., 2005) - inhibit IL-8 and VEGF secretion (Feoktistov et al., 2003)	PSB1115 PSB603 ATL801 Aminophylline** MRS1754*** IPDX	A2BR	BAY60-6583 NECA** PHPNECA**	- Increase tumor growth, proliferation, angiogenesis and metastasis (Beavis et al., 2013; Koszałka et al., 2016; Stagg et al., 2010) - Induce mitochondrial signaling pathway of apoptosis (Hajiahmadi et al., 2015) - Increase VEGF, cAMP , IL-10 (Iannone et al., 2013; Ryzhov et al., 2008; Sorrentino et al., 2015; Wei et al., 2013) - Decrease LDH, Caspase-3 (Wei et al., 2013) - Decrease cell viability and increase apoptosis (Hajiahmadi et al., 2015; Long et al., 2015) - Increase tumor cell migration (Stagg et al., 2010) - Increase MDSC infiltration in tumor (Sorrentino et al., 2015)
- Increase proliferation, tumor growth and angiogenesis (Bar-Yehuda et al., 2001; Nakamura et al., 2006; Yoshikawa et al., 2008) - Decrease proliferation of bone marrow cells (Bar-Yehuda et al., 2001)	MRS1191 MRS1220 MRS1523	A3R	IB-MECA Cl-IB-MECA Cordycepin	- Decrease NF-κB and Wnt pathways (Bar-Yehuda et al., 2008; Fishman et al., 2001; Fishman et al., 2006; Fishman et al., 2004; Fishman et al., 2002; Harish et al., 2003; Van Troostenburg et al., 2004) - Increase infiltration of pro-inflammatory macrophages (Fishman et al., 2004; Koszałka et al., 2016) - Increase anti-tumor function of NK (Harish et al., 2003; Mirandola et al., 2004; Morello et al., 2011)

				- Increase recruitment and activation of cytotoxic CD 8+ T cells in tumor site (Montinaro et al., 2012; Morello et al., 2011) - Increase the number of mature and active dendritic cells in tumor site (Morello et al., 2011) - Increase IL-12, TNF-α and IFN-γ (Harish et al., 2003; Morello et al., 2011) - Induce cytotoxic signals in tumor cells (Panjehpour and Karami-Tehrani, 2007) - Decrease tumor growth, proliferation and metastasis (Brambilla et al., 2000; Harish et al., 2003; Iannone et al., 2013; Koszałka et al., 2016; Montinaro et al., 2012; Morello et al., 2011) (Bar-Yehuda et al., 2008; Ohana et al., 2003) - Induce apoptosis by upregulation of the pro-apoptotic proteins BAD, BAX and Caspase-3 (Aghaei et al., 2011; Bar-Yehuda et al., 2008) - Tumor inhibitory effects (Bar-Yehuda et al., 2008; Iannone et al., 2013; Koszałka et al., 2016; Montinaro et al., 2012; Morello et al., 2011; Ohana et al., 2003) - Help to growth of normal cells (Bar-Yehuda et al., 2002; Ohana et al., 2003) - Enhance the myelopoiesis (Bar-Yehuda et al., 2002; Ohana et al., 2003) - Inhibit the myelotoxic effects of chemotherapy (Bar-Yehuda et al., 2002) - Cardioprotective effect during chemotherapy (Zhang et al., 2009)

[*]These effects might be varying or even inverting by the tumor type, tumor stages, types and doses of used agonist/antagonist
[**]Non-selective ligands
*** Specific A2BR antagonist at low dose but not specific at high dose (Zhou et al., 2015)

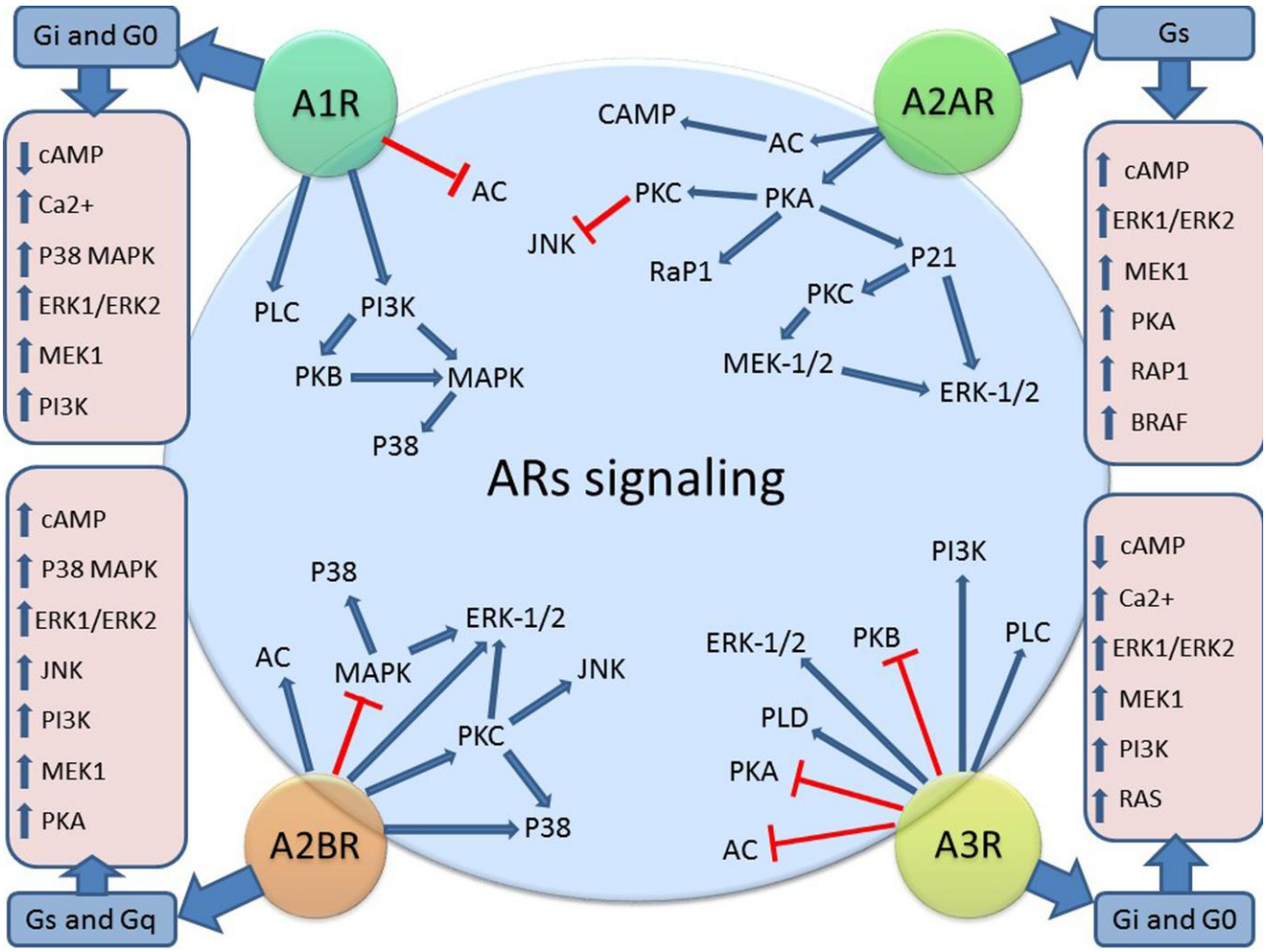

Figure 1

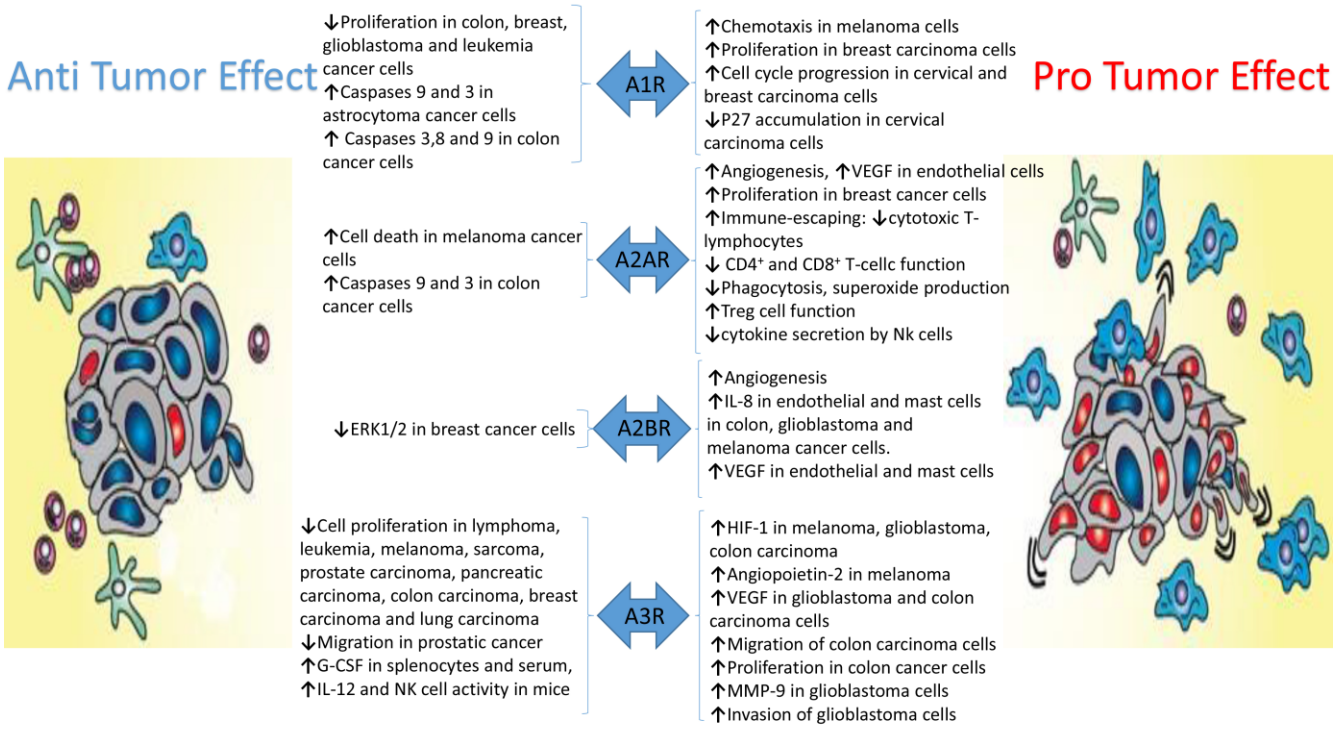

Figure 2